

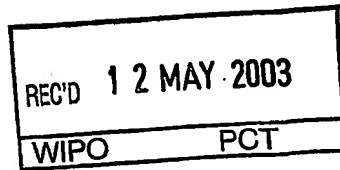
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10/510147

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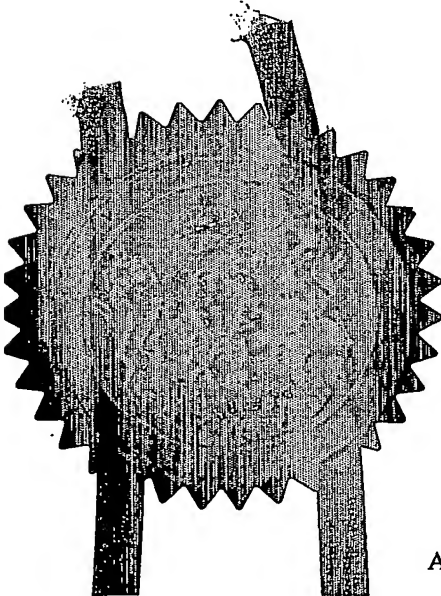
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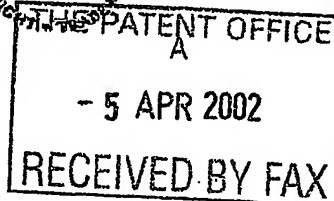
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05APR02 E708917-1 D02956  
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## 1. Your reference

57767 GB 002

## 2. Patent application number

(The Patent Office will fill in this part)

0207899.6

- 5 APR 2002

## 3. Full name, address and postcode of the or of each applicant (underline all surnames)

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

3M Innovative Properties Company

3M Center / 220 12W 01

1-94 and McKnight Road

St. Paul

MN 55144-1000, USA

USA / Delaware

766 4097001

## 4. Title of the invention

Formoterol and Ciclesonide Aerosol Formulations

## 5. Name of your agent (if you have one)

Lorraine Alcandri-Hachgenei

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

OIPC Neuss

c/o Dept. of Legal Affairs

3M United Kingdom PLC

3M House

P.O. Box 1, Market Place

RG12 1JU Bracknell, Berkshire

83 57741 001

Patents ADP number (if you know it)

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Country

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## 7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing  
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## 8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer Yes if

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I/We request the grant of a patent on the basis of this application.

*Lorraine Alexandri-Hachgenel*  
Signature

Date

Lorraine Alexandri-Hachgenel

05 April 2002

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Paula Roan  
Dept. of Legal Affairs  
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**Patents Form 1/77**

## FORMOTEROL AND CICLESONIDE AEROSOL FORMULATIONS

### Field of the Invention

- 5 This invention relates to medicinal aerosol formulations and in particular to aerosol formulations containing formoterol in suspension and ciclesonide in solution suitable for administration to the respiratory tract.

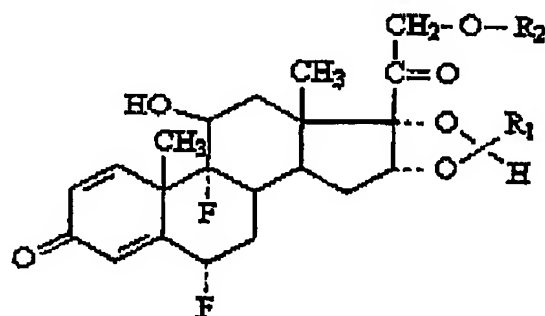
### Background

10

Formoterol, N-[2-hydroxy-5-(1-hydroxy-2-(2-(4-methoxyphenyl)-1-methylethyl) amino)ethyl) phenyl] formamide, particularly in the form of its fumarate salt, is a bronchodilator used in the treatment of inflammatory or obstructive airways diseases.

15

GB-2247680 discloses pregna-1,4-diene-3,20-dione-16-17-acetal-21 esters and their use in the treatment of inflammatory conditions. The compounds have the general structure:



20

wherein  $R_1$  is 2-propyl, 1-butyl, 2-butyl, cyclohexyl or phenyl; and  $R_2$  is acetyl or isobutanoyl. Ciclesonide is  $11\beta$ ,  $16\alpha$ , 17, 21-tetrahydroxypregna 1,4-diene-3,20-dione, cyclic 16,17-acetal with cyclohexanecarboxaldehyde, 21-

isobutyrate having the structure of general formula given above without fluorine atoms and in which  $R_1$  is cyclohexyl and  $R_2$  is isobutanoyl.

DE 19541689 discloses the combined use of ciclesonide with a  $\beta$ 2-  
5 sympathomimetic, for the treatment of respiratory disorders. It is stated that such combinations are suitable for long-term therapy and provide good local and anti-inflammatory effect in conjunction with quick relief of bronchospasms and without systemic side effects. As an exemplary formulation, DE 19541689 discloses a suspension aerosol composition consisting of  
10 ciclesonide (3.7 g) and formoterol fumarate dihydrate (1.1g) as micronized particles dispersed in trichlorofluoromethane (1.99 kg), dichlorodifluoromethane (3.00 g) with sorbitan trioleate (15.5 g).

However at the time of the filing of DE 19541689 in 1995, these  
15 chlorofluorocarbon (CFC) propellants were generally understood to provoke the degradation of stratospheric ozone. Thus there was at that time and there still is a general need to provide aerosol formulations for medicaments, which employ so-called "ozone-friendly" propellants. A class of propellants which are believed to have minimal ozone-depleting effects in comparison to  
20 conventional CFCs comprise hydrofluorocarbons, in particular 1,1,1,2-tetrafluoroethane ("HFA 134a") and 1,1,1,2,3,3,3-heptafluoropropane ("HFA 227"). A number of medicinal aerosol formulations using such propellant systems are disclosed in, for example, EP 0372777, W091/04011, W091/11173, W091/11496, W091/14422, EP 0 504 112, W093/11745, WO  
25 93/11747, WO 97/47286 and WO 98/52542 (all hereby incorporated by reference). These applications are all concerned with the preparation of pressurised aerosols for the administration of medicaments and seek to overcome problems associated with the use of this new class of propellants, in particular the problems of stability associated with the pharmaceutical  
30 formulations prepared.

EP-A-0504112, for example, discloses a pharmaceutical composition for aerosol use containing: (a) a liquefied propellant gas or propellant gas mixture with a vapor pressure exceeding 1 bar but less than 6 bar (20°C) from the  
5 unsubstituted or partially to completely fluorinated hydrocarbon group; (b) a non-ionic tensile of the monoacetylated or diacetylated monoglyceride group; (c) a pharmaceutical active substance or combination of active substances, and, if necessary, (d) other common pharmaceutical accessory substances suitable for aerosol formulations. It is stated the basic purpose of  
10 that invention was to find a special accessory suspending substance for active substances in aerosol formulations, which dissolves better in liquefied "alternative" propellant gases than the accessory suspending substances hitherto recognized and used. It is stated that surprisingly, it was discovered, in solving this problem, that non-ionic tensides of the monoacetylated or  
15 diacetylated monoglyceride group are very soluble in the "alternative" propellant gases mentioned, particularly in HFA 227, are beneficial to the production of homogenous suspensions, and also have outstanding metering valve lubrication properties. Some of the examples of EP-A-0 504 112 disclose formulations comprising formoterol fumarate.

20

WO 93/11747 discloses a pharmaceutical suspension formulation suitable for aerosol administration, consisting essentially of a therapeutically effective amount of a drug and a propellant selected from the group consisting of HFA 134a, HFA 227, and a mixture thereof, the formulation being further  
25 characterized in that it exhibits substantially no growth in particle size or change in crystal morphology of the drug over a prolonged period, is substantially and readily redispersible, and upon redispersion does not flocculate so quickly as to prevent reproducible dosing of the drug. The application specifically discloses formulations of formoterol fumarate in HFA  
30 134a, HFA 227 and 1:1 mixtures of HFA 134a and HFA 227. The

formulations do not contain surfactants or ethanol. It is stated that mixtures of HFA 134a and HFA 227 may be adjusted for density matching with the drug.

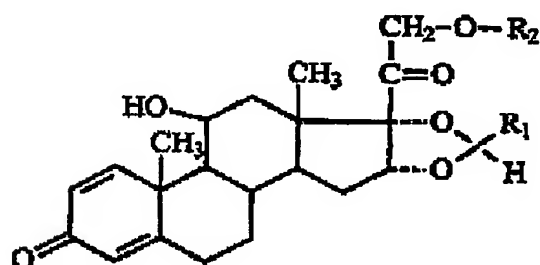
WO 93/11745 discloses pharmaceutical aerosol formulations, substantially  
5 free of surfactant containing fluorocarbon or hydrogen-containing  
chlorofluorocarbon propellants and up to 5% of a polar co-solvent. Preferred  
propellants are HFA 134a and HFA 227 which are preferably used alone. The  
preferred polar co-solvent is ethanol and it is stated that in general only small  
quantities e.g. 0.05 to 3.0% w/w of polar co-solvent are required to improve  
10 the dispersion and the use of quantities in excess of 5% w/w may  
disadvantageously tend to dissolve the medicament.

WO 97/47286 discloses a pharmaceutical suspension formulation suitable for  
aerosol administration, consisting essentially of: (a) from 0.0025 to 0.1% w/w  
15 of micronized formoterol, or an acid addition salt thereof and (b) from 0.1 to  
5.0% w/w ethanol, (c) HFA 134a, HFA 227 or a mixture of HFA 227 and HFA  
134a and optionally (d) a surfactant other than a monoacetylated or  
diacetylated monoglyceride, the formulation being further characterized in that  
it exhibits substantially no growth in particle size or change in crystal  
20 morphology of the drug over a prolonged period, is substantially and readily  
redispersible, and upon redispersion does not flocculate so quickly as to  
prevent reproducible dosing of the drug. The application specifically discloses  
formulations comprising formoterol fumarate dispersed in HFA 134a, HFA  
227 or mixtures thereof and 1 to 3% ethanol. It is stated that it is important to  
25 ensure the formoterol fumarate does not come into contact with high  
concentrations e.g. above 10% w/w, of ethanol since the drug would dissolve  
leading to instability and crystal growth problems in the final formulation and  
that the maximum concentration of ethanol during formulation is preferably  
less than 5%. It is stated that aerosol compositions consisting of formoterol  
30 fumarate, HFA 134a and ethanol have proved to be extremely sensitive to

5

ethanol concentration and an ethanol concentration of 3.5% w/w may cause unacceptable crystal growth.

WO 98/52542 discloses a pharmaceutical compositions comprising a  
5 therapeutically effective amount of a compound of the formula (I):



in which: R<sub>1</sub> is 1-butyl, 2-butyl, cyclohexyl or phenyl and R<sub>2</sub> is acetyl or  
10 isobutanoyl, and a hydrofluorocarbon propellant, preferably selected from  
1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and a mixture  
thereof, and cosolvent, preferably ethanol, in an amount effective to solubilize  
the compound of formula (I) and optionally a surfactant. The application  
specifically discloses solution formulations comprising ciclesonide (1 to 5  
16 mg/ml) in HFA 134a, HFA 227 or mixtures of HFA 134a and HFA 227 and 5  
to 20% by weight ethanol.

Despite the various approaches used in formulating drugs for use in aerosol  
inhalation, a number of serious difficulties and uncertainties are still often  
20 encountered in attempting to develop a physically and chemically stable CFC-  
free formulation that reliably delivers an accurate dose of drug having the  
proper particle size range.

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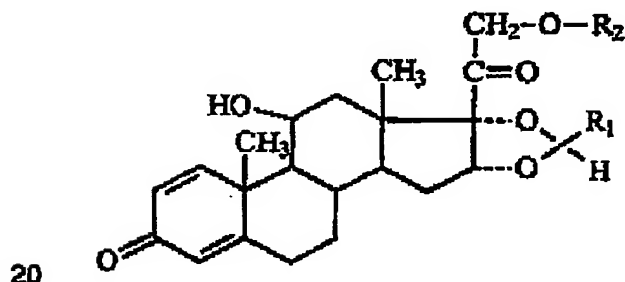


### Summary of the Invention

There is a need for a CFC-free medicinal aerosol product containing formoterol and ciclesonide (or similar molecules) that is chemically and physically stable and that is suitable for delivery to the respiratory system of a patient.

Surprisingly it has been found that it is possible to provide physically and chemically stable formulations of formoterol fumarate in suspension and ciclesonide in solution at therapeutic effective concentrations in HFA 134a and/or HFA 227 propellant.

Accordingly in one aspect of the present invention there is provided a pharmaceutical aerosol composition comprising particles of formoterol or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, said particles being suspended in the formulation;  
a compound of the formula (I):



in which: R<sub>1</sub> is 1-butyl, 2-butyl, cyclohexyl or phenyl and R<sub>2</sub> is acetyl or isobutanoyl, said compound of formula (I) being dissolved in the formulation;  
and

a propellant selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and a mixture thereof.

WO 99/28296 and WO 99/65464 disclose medicinal aerosol formulations  
5 comprising a first drug suspended in propellant and a second drug dissolved in the formulation. However, ciclesonide or a similar molecule is not disclosed as a drug in either document, formoterol is not disclosed in WO 99/65644, and neither document discloses such a formulation containing formoterol or a  
10 pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and a compound of formula (I).

Due to the reported sensitivity of particulate formoterol, in particular formoterol fumarate, dispersed in HFA 134a and/or HFA 227 propellant to  
15 ethanol, it was considered not feasible to formulate particulate formoterol in combination with therapeutically effective amounts of ciclesonide (or similar molecules) at levels of ethanol that would be needed for complete dissolution of ciclesonide (or similar molecules).

Surprisingly, it was found possible to successfully formulate the drug  
20 combination at levels of ethanol considered unsuitable for one of the drugs. In particular, it was found that ethanol can be present in an amount effective to completely solubilize a compound of formula (I), such as ciclesonide, yet without the formoterol or a pharmaceutically acceptable salt, solvate or  
25 physiologically functional derivative thereof, such as formoterol fumarate, exhibiting detrimental growth in particle size or change in crystal morphology over a high stress storage interval.

The amount of ethanol in the formulation is advantageously present in a  
30 amount from 3 to 20% by weight, preferably from 5 to 16% by weight, more preferably 5 to 12 % by weight, most preferably 5 to 10% by weight.

Preferably the propellant comprises HFA 134a, more preferably HFA 134a is applied as the only propellant component.

- 5 To further enhance physical stability and homogeneity of the dispersion of formoterol or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, the formulations may advantageously comprise a particulate bulking agent having a mass median diameter of less than one micron.

10

- Formulations according to the invention are particularly suitable for use in inhalation therapy, in which a therapeutically effective amount of the formulation is delivered to the lung by oral or nasal inhalation, more particularly for prophylaxis or treatment of a clinical condition for which a  
15 selective  $\beta_2$ -adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated. The present invention also provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective  $\beta_2$ -adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated, which comprises administration via inhalation a therapeutically  
20 effective amount of the formulation as described above. In particular, the present invention provides such methods for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

25

In another aspect of the present invention, there is provided a dispenser comprising an aerosol vial equipped with a dispensing valve containing a formulation as described above.

30

**Detailed Description**

It is to be understood that the present invention covers all combinations of particular and preferred aspects of the invention described herein.

5 As would be appreciated by the skilled person, formoterol includes two asymmetric centres. The present invention includes each isomer of formoterol either in substantially pure form or admixed in any proportions or a racemic mixture, particularly the (R, R)-isomer. The enantiomers of formoterol have been described previously, for example, in WO 98/21175 and US5795564.

10

By the term "physiologically functional derivative" is meant a chemical derivative of formoterol having the same physiological function as the free compound, for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives  
15 include esters.

Suitable salts according to the invention include those formed with both organic and inorganic acids. Pharmaceutical acceptable acid addition salts include but are not limited to those formed from hydrochloric, hydrobromic, 20 sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-toluenesulphonic, benzenesulphonic, isethionic, and naphthalenecarboxylic, such as 1-hydroxy-2-naphthalenecarboxylic acids.

25 Pharmaceutically acceptable esters of formoterol may have a hydroxyl group converted to a C<sub>1-8</sub> alkyl, aryl, aryl C<sub>1-8</sub> alkyl, hetaryl (such as furanyl) or amino acid ester.

In preferred embodiments of the invention, formoterol fumarate (suitably as in the form of the dihydrate) is applied in combination with the compound of formula (I).

5 The compound of formula (I) is preferably ciclesonide.

Hereinafter, the term "formoterol" is understood to include formoterol or a pharmaceutical acceptable salt, solvate, or physiologically functional derivative thereof, preferably formoterol fumarate, more preferably formoterol fumarate dihydrate, while the term "compound of formula (I)" includes preferably ciclesonide.

Formoterol and the compound of formula (I) are generally present in a formulation of the invention in a therapeutically effective amount.

15

The amount of formoterol and compound of formula (I), which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the subject under treatment, and the particular disorder or disease being treated. Suitably, the pharmaceutical formulations which are suitable for inhalation according to the invention comprise formoterol and a compound of formula (I) in amounts such that one or two actuations provide a therapeutically effective dose, for example, a dose of formoterol of 1 mcg to 50 mcg, preferably 3 mcg to 25 mcg, more preferably 4 mcg to 12 mcg and a dose of the compound of Formula (I) of 20 mcg to 1 mg, preferably 35 mcg to 500 mcg, more preferably, 50 mcg to 200 mcg. Various dosing of the individual drugs can be advantageously combined for particular disorders or subjects under treatment. For example a formoterol dosing, such as 6 mcg per actuation can be combined with a low, medium and high strength dosage of the compound of formula (I), e.g. 50, 100 and 200 mcg per actuation.

30

Preferably formoterol constitutes about 0.06 to about 0.60 mg per ml, more preferably about 0.08 to about 0.30 mg per ml, even more preferably about 0.10 to about 0.20 mg per ml, most preferably about 0.120 to about 0.132 mg per ml of the formulation.

5

The particles of formoterol are generally micronised particles or particles processed by other methods, preferably having a mass median diameter equal to or greater than 1 micron, more particularly from 1 to 10 micron, even more particularly from 1 to 5 micron. Smaller particles having a mass median diameter of less than one micron may also be suitable.

10

The compound of formula (I) is generally present at a concentration of from about 0.5 to about 8 mg per ml, preferably about 1 to about 5 mg per ml, most preferably about 1 to about 4 mg per ml of the formulation. Advantageously, the compound of formula (I) may be formulated at a low, medium and high strength dosing, preferably at 1 mg per ml, 2 mg per ml and 4 mg per ml of the formulation.

15

The formulations of the invention typically comprise an adjuvant to aid the complete dissolution of the compound of formula (I). The level of adjuvant is desirably selected such that the compound of formula (I) is completely soluble in the aerosol formulation over the temperature range likely to be encountered by the product during storage and use, e.g. 10 to 35°C, while the suspended formoterol exhibits substantially no growth in particle size (e.g. a growth of 25% or less (e.g. based on mass median diameter as determined by laser diffraction) after high stress cycling (i.e. 4 temperature cycles in a 24 hour period, where one cycle is defined as: 4°C at a duration of 2 h; ramping up from 4 to 40°C in 1 h; 40°C for 2 h and ramping down from 40 to 4°C in 1 h) over a period of 10 days). Suitable adjuvants are disclosed in EP-A-0372777. Ethanol is a preferred adjuvant. When ethanol is applied as adjuvant, it has

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25

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been found that ethanol is desirably present in an amount from 3 to 20% by weight, preferably from 5 to 16% by weight, more preferably 5 to 12 % by weight, most preferably 5 to 10% by weight of the formulation.

- 5 The propellant is selected from HFA 134a, HFA 227 and mixtures thereof. Preferably the propellant comprises HFA 134a, either in a mixture with HFA 227 or more preferably as the only propellant component. Variation of the concentration of HFA 134a and HFA 227 in mixtures allows adjustment of the density of the propellant to match the density of the suspended formoterol.
- 10 Density matching may decrease the rate of sedimentation or creaming of the suspended formoterol particles.

- The aerosol formulations of the invention may preferably contain surfactant, more preferably a surfactant other than a monoacetylated or diacetylated monoglyceride, for e.g. imparting a flocculant effect for the suspended formoterol, which may allow less migration of the drug to and from the metering chamber. When surfactant is included in a formulation it is generally present in an amount of about 0.001 % to 0.010 % by weight of the formulation. Suitable surfactants are well known in the art and include
- 15 sorbitan trioleate, oleic acid and lecithin. Surfactants, such as oligolactic acid derivatives disclosed in WO94/21228 and WO94/21229, and other surfactants disclosed in the literature may be used. As a surfactant oleic acid is preferred. The formulations are preferably free of other excipients.

- 25 It has been found that a bulking agent having a mass median diameter of less than one micron may be applied to enhance physical stability and homogeneity of the suspension of the formoterol particles. It is not necessary for the surface of the bulking agent or the drug to be coated with a surface modifier to achieve improved stability. In particular it has been found that the
- 30 application of such a nano-sized bulking agent aids in minimizing the

tendency of formoterol to cream or sediment, depending on the density difference of the drug and the propellant. More particularly, it has been found that the application of such a nano-sized bulking agent aids in maintaining a high sediment volume (i.e. minimizing a dense packing of the sediment) and/or the formation of a voluminous, loosely flocculated matrix, enhancing the re-dispersion and/or de-flocculation of the drug upon agitation.

The mass median diameter of the bulking agent can advantageously be as low as 300 nanometers, more desirably as low as 250 nanometers, even more desirably the mass median diameter is in the range of 100 to 250 nanometers and most desirably in the range of 150 to 200 nanometers.

Mass median diameter (which is equivalent to volume median diameter) can be determined using any conventional particle size measurement method known to those skilled in the art. Suitable methods include for example laser diffraction, photon correlation spectroscopy (e.g. using a spectrometer available under the trade designation Brookhaven PCS from Brookhaven Inc.), spinning disc centrifuging (using an instrument available under the trade designation CPS Disc Centrifuge from Chemical Process Specialists Inc.) and scanning electron microscopy (SEM). Mass median diameter is preferably determined by laser diffraction, photon correlation spectroscopy or spinning disc centrifuging, more preferably by laser diffraction, more particularly laser diffraction using an analyser available under the trade designation Malvern Mastersizer 2000 laser light diffraction particle size analyser from Malvern Instruments Ltd.

Preferred bulking agents include lactose, DL-alanine, ascorbic acid, glucose, sucrose D(+)-trehalose as well as their various hydrates, anomers and/or enantiomers. Lactose including its various forms, such as  $\alpha$ -lactose monohydrate and  $\beta$ -lactose and alanine are more preferred. Lactose, in



particular in its  $\alpha$ -lactose monohydrate form, is most preferred as a bulking agent due to e.g. processing considerations. Other suitable bulking agents include other saccharides e.g. D-galactose, maltose, D(+)-raffinose pentahydrate, sodium saccharin, polysaccharides e.g. starches, modified  
5 celluloses, dextrans or dextrans, other amino acids e.g. glycine, salts e.g. sodium chloride, calcium carbonate, sodium tartrate, calcium lactate, or other organic compounds e.g. urea or propylidone.

Based on the amount of formoterol in the formulation, the weight ratio of  
10 formoterol to bulking agent is generally in the range 1:0.1 to 1:25, preferably 1:2 to 1:15, even more preferably 1:4 to 1:12 and most preferably about 1:10.

The bulking agent may be reduced to the required particle size by any convenient method, e.g. grinding, air-jet milling etc. Preferably the bulking  
15 agent is reduced to nanoparticle size in a high pressure homogenizer, such as the commercially available Avestin Emulsiflex homogenizers and the Microfluidics Microfluidizer homogenizers. In the processing with high pressure homogenizers, certain bulking agents can be reduced to the desired particle size using lower pressures than that applied for other bulking agents.  
20 For example, it has been found that lactose, more specifically  $\alpha$ -lactose monohydrate, can be effectively reduced to the desired particle size using pressures between about 10,000 and about 21,000 psi, while for effective particle size reduction of alanine or sucrose higher pressures of about 25,000 psi for repeated passes were applied.

25

The bulking agent may be prepared in a slurring aid which is a low volatility solvent such as ethanol. It may be prepared in a slurring aid which is a component of the final aerosol formulation, or it may be prepared in a solvent that is subsequently removed or exchanged with a component of the

formulation by some process such as centrifugation and decanting, dialysis, evaporation etc.

It is particularly convenient to use a slurring aid in the high pressure  
5 homogenizer which is a low volatility component of the aerosol formulation  
and after particle size reduction has been achieved the slurry may be  
adjusted if necessary, e.g. concentrated by centrifugation, decanting etc.  
Whilst it has been found that slurries with excessively high powder loadings  
may be difficult to process due to their rheological properties, it is generally  
10 advantageous to process slurries with powder loading concentrations which  
approach this processing limit in order to achieve the desired particle size  
distribution in the shortest processing time. Thus, the weight ratio of  
liquid:solid is generally in the range 5:1 to 100:1, preferably 5:1 to 20:1, and  
most preferably about 8:1 to about 10:1.

15 The present invention also provides a method of preparing a formulation  
according to the invention, the method comprising the steps of (i) providing a  
solution of the compound of formula (I) in HFA 134a and/or HFA 227 and (ii)  
dispersing particles of formoterol in the solution. For formulations containing  
20 adjuvant, in particular ethanol, typically step (i) includes sub-steps of mixing  
the compound of formula (I), and if applicable surfactant, in an appropriate  
amount of adjuvant and adding the resultant to an appropriate amount of HFA  
134a and/or HFA 227 in liquid form (chilled to below its boiling point or range).  
Step (ii) typically includes the following sub-steps: removing a portion of the  
25 compound of formula (I) containing solution, adding particulate formoterol to  
this portion to form a formoterol-containing slurry, mixing the formoterol-  
containing slurry, preferably after high shear mixing thereof, in the remaining  
portion of the original compound of formula (I) containing solution.

For formulations containing a nano-sized bulking agent, a preferred method of preparing a formulation comprises the steps of (i) forming a slurry of bulking agent with a component of the formulation; (ii) subjecting the slurry to high pressure homogenization; and (iii) combining the resulting slurry with other components of the aerosol formulation. For formulations containing ethanol, the slurry of bulking agent may be advantageously prepared with an appropriate amount of ethanol. The slurry is subjected to high pressure homogenization prior to adding it to the remainder of the formulation. During manufacture, typically the slurry of bulking agent is then added to a solution of the compound of formula (I) in an appropriate amount of HFA 134a and/or HFA 227 and, if applicable an appropriate amount of adjuvant (e.g. ethanol) and/or surfactant. (Said solution prepared in a similar manner as described above.) In a subsequent step, particles of formoterol are then dispersed in compound of formula (I) containing liquid. As described above, this is typically achieved by taking off a portion of the compound of formula (I) containing liquid, in an intermediate step, and adding particulate formoterol to this portion to form a slurry of formoterol. This formoterol slurry, typically after high shear mixing thereof, is then re-added and mixed with the remaining portion of the original compound of formula (I) mixture.

20

Dispensers comprising an aerosol vial equipped with conventional dispensing valves, preferably metered dose valves, can be used to deliver formulations of the invention. Conventional dispensers and aerosol vials can be used to contain a formulation of the invention. However certain vials may enhance the chemical stability of certain formulations of the invention. Therefore it is preferred to contain a formulation of the invention within a glass aerosol vial or a metal, in particular aluminum, vial having an interior surface coated with a polymer, in particular a fluorocarbon polymer. Advantageously other internal surfaces, in particular such surfaces of components of the valve, or all of the internal surfaces of the dispenser may be also coated with a polymer, in

30

particular a fluorocarbon polymer. Suitable fluorocarbon polymers include fluorocarbon polymers, which are made of multiples of one or more of the following monomeric units: tetrafluoroethylene (PTFE), fluorinated ethylene propylene (FEP), perfluoroalkoxyalkane (PFA), ethylene tetrafluoroethylene (ETFE), vinylidene fluoride (PVDF), and chlorinated ethylene tetrafluoroethylene. Polymers, which have a relatively high ratio of fluorine to carbon, such as perfluorocarbon polymers e.g. PTFE, PFA, and FEP, are preferred; FEP is particularly preferred.

10 The valve may be any suitable metering valve with an outlet made from, for example stainless steel, acetal, nylon or polybutylene terephthalate and with seals made from nitrile or EPDM elastomer.

15 A formulation of the invention can be administered to the lung by oral or nasal inhalation. Oral inhalation is preferred, and conventional actuators for oral inhalation can be used in connection with a formulation of the invention. Good respirable doses can be achieved with an orifice diameter within the range of 0.2 to 0.6 mm, preferably in the range 0.24 to 0.47 mm, most preferably 0.28 to 0.35 mm.

20

The invention will be illustrated by the following Examples.

Materials used:

25  $\alpha$ -lactose monohydrate supplied under the trade designation Pharmatose 325M by DMV International Pharma was micronised by fluid energy milling in a single pass (referred to here and in the following as "micronised lactose monohydrate"). Micronised lactose monohydrate (100 g) was dispersed in Anhydrous Ethanol (840 g) using a Silverson high shear mixer. This  
30 dispersion was added to the product reservoir of an Avestin Emulsiflex C50

homogenizer, and recirculated for 20 minutes at 10,000 psi. The dispersion was then passed out of the homogenizer, after recirculation for 30 seconds, at 20,000 psi. The particle size was determined according to the following method.

5

#### Particle Size Analysis

For analysis of a Lactose/Ethanol slurry, a (0.5 ml) sample of the slurry, which was shaken for at least one minute to ensure homogeneity, was added to a  
10 solution of 0.05% Lecithin in Iso-octane (20 ml), and redispersed with mild ultrasonics for 1 minute.

The resulting suspension was introduced dropwise into the presentation cell (a Hydro 2000 SM small sample presentation cell) of a Malvern Mastersizer  
15 2000<sup>TM</sup> laser diffraction particle sizer until the obscuration was in the working range (between 10 and 12 with a red laser), and left to circulate for 1 minute to allow complete mixing and thermal equilibrium to be established. Ten readings were taken at 20 second intervals to establish that the particle size was stable. The General Purpose analysis model, as described in the  
20 Malvern Instruments Operators Guide, was used with refractive indices 1.533 (lactose), 1.392 (iso-octane) and absorbance 0.001 (lactose). The results are based on the average calculated results of 10 readings taken in succession. The procedure was performed twice.

Results of Particle Size Analysis by Malvern Mastersizer 2000

	Lactose
Units	Microns
d(v,0.1)	0.073
d(v,0.5) median	0.170
d(v,0.9)	1.259
D[4,3] volume weighted mean	0.455
Units	Percent
vol under 0.05 micron	2.10
vol under 0.10 micron	23.10
vol under 0.20 micron	57.48
vol under 0.50 micron	76.49
vol under 1.0 micron	86.56
vol under 2.0 micron	95.97
vol under 5.0 micron	99.54
vol under 10.0 micron	100.00
vol under 20.0 micron	100.00

Examples

## Example 1

Material	mg/ml	% w/w	Batch quantity (g)
FORMOTEROL FUMARATE dihydrate (micronised)	0.120	0.0101	0.1140
CICLESONIDE (micronised)	4.000	0.3362	3.7989
OLEIC ACID (VEGETABLE SOURCE) Ph.Eur/USNF	0.0595	0.0050	0.0565
Dehydrated Alcohol USP; Ethanol, Anhydrous Ph. Eur.	59.4913	5.0000	56.5000
PROPELLANT 134a,	1126.1561	94.6487	1069.5306
Total	1189.8269	100.0000	1130.0000

- 5 This formulation was prepared as follows. HFA 134a was weighed into a batching vessel and stored at  $-60^{\circ}\text{C}$ . Oleic acid and Ciclesonide were dissolved in Ethanol and the solution added to the batching vessel to produce a chilled blend. The formoterol fumarate was then dispersed in the chilled blend using a high shear mixer. The resulting chilled suspension was filled
- 10 into 10ml aluminium vials whose internal surface was lined with Fluorinated Ethylene Propylene (FEP) polymeric coating. The vials were immediately sealed with 50 ml metering valves. A fill weight of 11.3 g was used and 100 MDI units were prepared.

## 15 Example 2

Material	mg/ml	% w/w	Batch quantity (g)
FORMOTEROL FUMARATE dihydrate (micronised)	0.1200	0.0101	0.1140
CICLESONIDE (micronised)	4.0000	0.3362	3.7989
LACTOSE MONOHYDRATE Ph. Eur./USNF	1.2000	0.1009	1.1397
OLEIC ACID (VEGETABLE SOURCE) Ph.Eur/USNF	0.0595	0.0050	0.0565
Dehydrated Alcohol USP; Ethanol, Anhydrous Ph. Eur.	59.4913	5.0000	56.5000
PROPELLANT 134a,	1124.9561	94.5478	1068.3909
Total	1189.8269	100.0000	1130.0000

This formulation was prepared as follows. HFA 134a was weighed into a batching vessel and stored at  $-60^{\circ}\text{C}$ . Oleic acid and Ciclesonide were dissolved in 46.9265 g of the Ethanol. Nano-sized lactose/ethanol slurry (10.7132 g) as prepared above was added to the solution of oleic acid and Ciclesonide in ethanol, and this mixture added to the HFA 134a in the batching vessel at  $-60^{\circ}\text{C}$  to produce a chilled blend. The formoterol fumarate was then dispersed in the chilled blend using a high shear mixer. The resulting chilled suspension was filled into 10ml FEP-lined aluminium vials, which were immediately sealed with 50 mcl metering valves. A fill weight of 11.3 g was used and 100 MDI units were prepared.

#### Evaluation of Formulations

The suspension settling rates of the formulations of Examples 1 and 2 were compared after cold-transferring formulation from 5 MDI units (of each example) to 5 clear plastic PET vials by chilling the units to  $-60^{\circ}\text{C}$ , de-crimping the valves, pouring the contents into the PET vials and crimping on non-metering valves. After allowing the formulations in the clear vials to equilibrate to room temperature, they were compared by visual assessment. Here the physical characteristics were observed after the formulations were shaken and then left to stand. The formulation of Example 1 was seen to be homogeneous over a 10 minute standing period whereas the formulation of Example 2 sedimented during this period to form a sediment volume occupying approximately 30% of the total formulation volume. The formulations were re-examined after 18 hours standing and it was noted that the formulation of Example 1 had sedimented to form a sediment which occupied a volume of around 1% of the formulation volume, whereas the formulation of Example 2 still had a sediment volume occupying approximately 30% of the total formulation volume.



The above observations indicate the nano-sized lactose bulked formulation of Example 2 has far greater homogeneity after 18 hours standing than the corresponding non-bulked formulation of Example 1. The improved homogeneity of the formulation of Example 2 would be expected to provide greater uniformity of dosing in an MDI system.

#### Stability on Storage

MDI units from both Examples 1 and 2 were stored (in a valve up orientation) for 10 days at the following conditions: a) at temperature of 5°C; b) at temperature of 40°C and 75% relative humidity; and c) under temperature cycling between 4°C and 40°C with 4 temperature cycles in a 24 hour period (one cycle having the following phases: 4°C at a duration of 2 h; ramping up from 4 to 40°C in 1 h; 40°C for 2 h and ramping down from 40 to 4°C in 1 h).

For each Example, the contents of the three units from each storage condition were transferred to PET vials (as described above) and after allowing the formulation to equilibrate to room temperature examined visually (as described above). It was noted that there were no differences discernible in any of the formulations between any of the storage conditions.

The FEP-lined aluminium vials and valves were also examined and it was noted that there were no signs of crystal growth on the surfaces of the vial or valve and that there were no excessive levels of drug deposition.

Samples of Example 1 (transferred to PET vials) prior to storage and after storage at each condition were also evaluated for turbidity by using an optical measuring technique described in the Proceedings of Drug Delivery to the Lung VI p.10-13 (December 1995) printed by the Aerosol Society. To use the

optical technique, each vial was shaken vigorously for 20 seconds before insertion into the apparatus, and light transmission through the formulation was measured after 30 seconds. The measurements were achieved by reading off the voltage value obtained from the light receiving sensor set to a central position relative to the initial height of the suspension column. A voltage 12.13 V corresponded to complete transmission, while 0 V corresponded to complete opacity.

The turbidity results were as follows:

Light transmission reading (Volts)	Initial	5°C	40°C / 75% rh	Temperature cycling 4-40°C
Vial 1	2.78	3.09	2.72	2.98
Vial 2	2.92	2.97	3.04	2.86
Vial 3	2.90	-	2.74	3.02

The results indicate that the suspension showed no significant changes in turbidity indicating that formulations with combined active ingredients had a satisfactory level of particle size stability for the suspended formoterol fumarate.

#### Chemical Stability

MDI units from Example 2 were stored for 5 days at 50°C in both valve-up and valve-down orientations (two units at each orientation). The samples were then tested for ciclesonide related impurities by High Performance Liquid Chromatography and the following results were obtained:

Sample	% Impurity
1 (valve-up)	0.06
2 ( valve-up)	0.06
1 ( valve-down)	0.05
2 (valve-down)	0.05

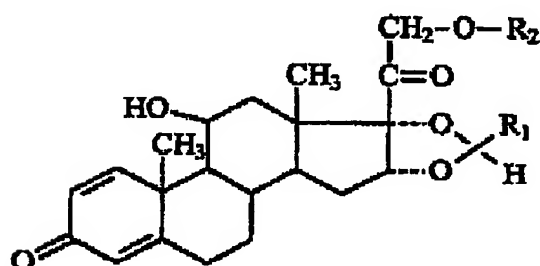
The results indicate that ciclesonide has a high degree of chemical stability in the example formulation; the value of 0.06% being just above the limit of quantification. Extrapolation of these results would suggest that this MDI system would have satisfactory long term (e.g. 2 to 3 years) chemical stability at 30°C.

## 5 CLAIMS

### 1. A pharmaceutical aerosol formulation comprising

particles of formoterol or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, said particles being suspended in the formulation;

10 a compound of the formula (I):



15 in which: R<sub>1</sub> is 1-butyl, 2-butyl, cyclohexyl or phenyl and R<sub>2</sub> is acetyl or isobutanoyl, said compound of formula (I) being dissolved in the formulation; and  
a propellant selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and a mixture thereof.

20 2. A pharmaceutical aerosol formulation according to claim 1, wherein the formoterol or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof is present in an amount of about 0.06 to about 0.60 mg per ml.

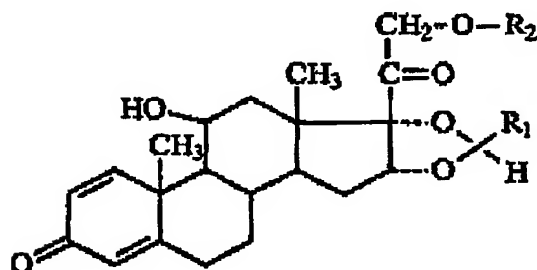
25 3. A pharmaceutical aerosol formulation according to claim 1 or claim 2, wherein the compound of formula (I) is present in an amount of about 0.5 to about 8 mg per ml.

4. A pharmaceutical aerosol formulation according to any one of claims 1 to 3, wherein the formoterol is in the form of formoterol fumarate.
5. A pharmaceutical aerosol formulation according to any one of claims 1 to 4, wherein the compound of formula (I) is ciclesonide.
- 5 6. A pharmaceutical aerosol formulation according to any one of claims 1 to 5, wherein the formulation further comprises ethanol.
7. A pharmaceutical aerosol formulation according to claim 6, wherein ethanol is present in an amount from 3 to 20% by weight of the formulation.
- 10 8. A pharmaceutical aerosol formulation according to any one of the claims 1 to 7, wherein the propellant is 1,1,1,2-tetrafluoroethane or a mixture of 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3,3-heptafluoropropane.
9. A pharmaceutical aerosol formulation according to any one of the claims 1 to 8, wherein 1,1,1,2-tetrafluoroethane is the only propellant component.
- 15 10. A pharmaceutical aerosol formulation according to any one of claims 1 to 9, wherein the formulation further comprises a bulking agent having a mass median diameter of less than one micron.
11. A pharmaceutical aerosol formulation according to claim 10, wherein the bulking agent has a mass median diameter of not more than 300 nm.
- 20 12. A pharmaceutical aerosol formulation according to claim 10 or claim 11, wherein the weight ratio of formoterol or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof to bulking agent is in the range 1:0.1 to 1:25.

13. A dispenser comprising an aerosol vial equipped with a dispensing valve,  
said aerosol vial containing a formulation according to any one of claims 1  
to 12.
- 5 14. A dispenser according to claim 13, wherein an interior surface of the  
aerosol vial is coated with a fluorocarbon polymer.
- 10 15. A method of preparing a formulation according to claim 1, the method  
comprising the steps of (i) providing a solution of the compound of formula  
(I) in 1,1,1,2-tetrafluoroethane and/or 1,1,1,2,3,3,3-heptafluoropropane  
and (ii) dispersing particles of formoterol or a pharmaceutically acceptable  
salt, solvate or physiologically functional derivative thereof in said solution.

**Abstract**

A pharmaceutical aerosol formulation comprising particles of formoterol or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, said particles being suspended in the formulation; a compound of the formula (I):



in which: R<sub>1</sub> is 1-butyl, 2-butyl, cyclohexyl or phenyl and R<sub>2</sub> is acetyl or isobutanoyl, said compound of formula (I) being dissolved in the formulation; and a propellant selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and a mixture thereof.

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